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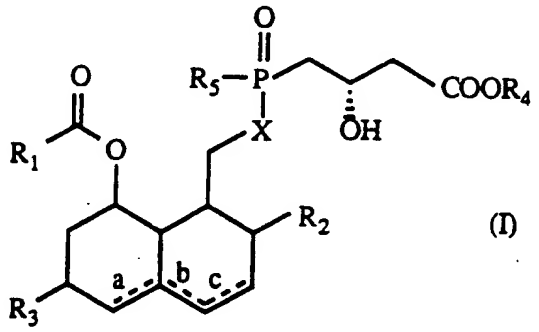

(I)

(57) Abstract

Compounds of general formula (I), wherein R_1 represents a C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-8})alkyl, C_{2-8} alkenyl, optionally C_{1-6} alkyl substituted phenyl, or optionally substituted phenyl(C_{1-6} alkyl) group; R_2 represents C_{1-8} alkyl group; R_3 represents a C_{2-6} alkenyl group or a C_{2-6} alkenyl group linked to an optionally substituted phenyl group; R_4 represents a hydrogen atom, a C_{1-5} alkyl group, a C_{1-5} alkyl group substituted with a group chosen from optionally substituted phenyl, dimethylamino or acetylamino; or a group M; R_5 represents a hydroxyl, -OM, or a C_{1-8} alkoxy group; M represents a cation capable of forming a pharmaceutically acceptable salt; X represents an oxygen atom, NH group or CH_2 group; a, b and c represent independently single or double bonds except that when a or c are double bonds then b represents a single bond; or pharmaceutically or veterinarily acceptable acid addition salts or hydrates thereof are potent inhibitors of HMG-CoA and are useful in the treatment or prevention of hypercholesterolaemia, hyperlipiproteinaemia and arteriosclerosis.

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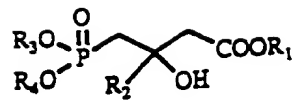
3-Carboxy-2-hydroxy-propane-phosphonic acid derivatives.

Coronary heart disease (CHD) is a major cause of death and disability in the Western World. Epidemiological evidence strongly indicates that hypercholesterolaemia - or more accurately, elevated levels of low-density lipoprotein cholesterol (LDL-C) - is a major risk factor for the development of CHD. Most cholesterol is synthesised de novo in the human body, in a multi-step process starting with acetyl-coenzyme A. The rate limiting step on this pathway is regulated by the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase) which catalyses the conversion of HMG-CoA to mevalonic acid. The enzyme is therefore a prime target for pharmacological intervention for the control of hypercholesterolaemia.

The present invention relates to novel 4-phosphono-3-hydroxy butanoic acid derivatives which inhibit the action of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) and as such are useful in inhibiting cholesterol biosynthesis, and also relates to hypercholesterolemic compositions containing these compounds.

FR-A-2596393 (Sanofi SA) discloses 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives including salts thereof which are useful as hypolipaemic agents and have the formula:



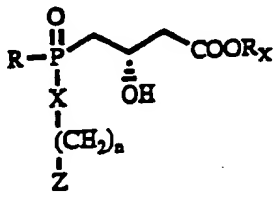
wherein

R_1 and R_2 = H, lower alkyl or optionally substituted aryl or arylalkyl;

R_3 and R_4 = H, lower alkyl or optionally substituted aryl or arylalkyl.

These compounds are reported to give greater reduction in cholesterol, triglyceride and phospholipid levels than meglutol.

DE-A-3817375 and US-A-4904646 (Squibb) disclose other 3-carboxy-2-hydroxy phosphonic acid derivatives and salts thereof as hypercholesterolemic agents having the formula:



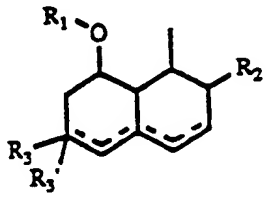
wherein

R_x is H, or alkyl;

R is OH, lower alkoxy or lower alkyl;
n is 1 or 2;

X is O, NH or CH_2,

Z is a hydrophobic anchor, specifically an optionally substituted aryl, an optionally substituted naphthyl, or a decalin radical of general formula:



R_1 = optionally substituted ester or ether

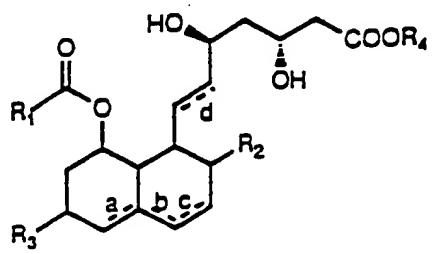
R_2 = lower alkyl

R_3, R_3' = independently H, OH, lower alkyl, alkylaryl, aryl.

No biological data is given describing the potency of these compounds. Compounds containing an R_3 alkenyl substituent are not described or claimed in these

documents.

Our copending application WO-A-9100280 discloses hypercholesterolemic agents of formula:



wherein

R_1 is alkyl, alkylaryl or aryl;

R_2 is H or lower alkyl;

R_3 is C_{2-6} alkenyl optionally substituted with an optionally substituted aryl moiety;

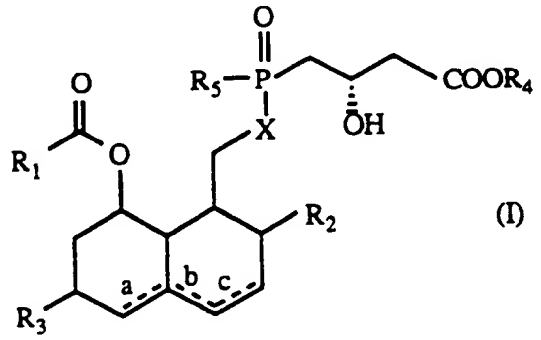
R_4 is H, lower alkyl, a pharmaceutically acceptable salt or an internal δ-lactone;

a, b, c and d are single or double bonds except that when a or c is double then b is single.

This document discloses that introduction of certain R_3 alkenyl substituents increases the HMG CoA reductase inhibitory activity of these compounds relative to mevinolin in which R_3 is methyl.

Compounds which incorporate both R_3 alkenyl substituents on the decalin and a phosphonyl group in the glutaryl-like side-chain are new. The present invention provides these novel decalin-based compounds which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and therefore are useful in the treatment or prevention of hypercholesterolaemia, hyperlipiproteinaemia and arteriosclerosis, particularly atherosclerosis.

According to the first aspect of the invention, there is provided a compound of general formula I



(I)

wherein

R_1 represents a C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-8})alkyl, C_{2-8} alkenyl, optionally C_{1-6} alkyl substituted phenyl, or optionally substituted phenyl(C_{1-6} alkyl) group;

R_2 represents C_{1-8} alkyl group;

R_3 represents a C_{2-6} alkenyl group or a C_{2-6} alkenyl group linked to an optionally substituted phenyl group;

R_4 represents a hydrogen atom, a C_{1-5} alkyl group, or a C_{1-5} alkyl group substituted with a group chosen from optionally substituted phenyl, dimethylamino or acetylamino or a group M;

R_5 represents a hydroxyl, -OM, or a C_{1-8} alkoxy group;

M represents a cation capable of forming a pharmaceutically acceptable salt;

X represents an oxygen atom, NH group or CH_2 group;

a, b and c represent independently single or double bonds except that when a or c are double bonds then b represents a single bond;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

As used herein, the term "C_{1-8} alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to eight carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, heptyl and octyl.

As used herein, the term "C_{1-5} alkyl" refers to a straight chain or branched chain hydrocarbon group having from one to five carbon atoms. Illustrative of such groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and pentyl.

As used herein, the term "C_{1-6} alkyl" refers to a straight chain or branched chain hydrocarbon group having from one to six carbon atoms. Illustrative of such groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and hexyl.

As used herein, the term C_{2-8} alkenyl refers to straight chain or branched chain hydrocarbon groups having from two to eight carbon atoms and having in addition one or more double bonds, of either E or Z stereochemistry where applicable. This term would include for example vinyl, (E)-prop-1-enyl, (Z)-prop-1-enyl, but-3-enyl, (E)-1-methylpent-1-enyl, 5-hexenyl and oct-7-enyl.

The term "C_{2-6} alkenyl" refers to a straight chain or branched chain hydrocarbon moiety having two to six carbon atoms and possessing an E or Z double bond. This includes for example, vinyl, (E)-prop-1-enyl, (Z)-prop-1-enyl, but-3-enyl, (E)-1-methylpent-1-enyl, and 5-hexenyl. Cognate terms (such as "C_{2-6}" alkenoxy) are to be construed accordingly.

The term "C_{3-8} cycloalkyl" refers to a saturated alicyclic moiety having from 3 to 8 carbons arranged in a ring and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

The term "optionally substituted phenyl group" means substituted with up to four substituents each of which may be C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, thiol, amino, halo, (including fluoro, chloro, bromo, and iodo),

trifluoromethyl or nitro.

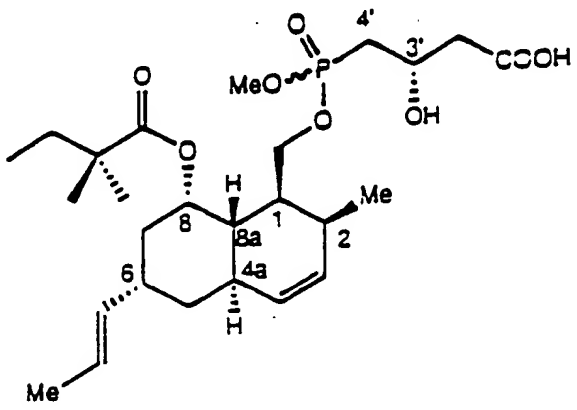
As used herein, the term "C_{1-6} alkoxy" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

The phrase "a pharmaceutically acceptable salt" as used herein and in the claims is intended to include non-toxic alkali metal salts such as sodium, potassium, calcium and magnesium, the ammonium salt and salts with non-toxic amines such as trialkylamines, dibenzylamine, and other amines which have been or can be used to form salts of carboxylic and phosphonic acids.

In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral centre. The invention is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof. The phosphorus atom forms an additional chiral centre and the invention includes both diastereoisomers at the phosphorus atom.

Disregarding any asymmetric centres which might be present in substituents R_{1-6}, the preferred relative and absolute stereochemistry is as shown in the structure below. The Cahn, Ingold, Prelog designations for this compound are 1S, 2S 4aR, 6S, 8S, 8aS, and 3'S. Both diastereomers at phosphorus are equally preferred.

It should be noted that the preferred diastereomers of other compounds of the invention may differ in their R-S designations because of the manner in which the sequence rules are determined.



Clearly in compounds in which a or b (in the general formula) are double bonds, the carbon atom labelled C_{4a} will not be an asymmetric centre.

Preferred compounds include those in which independently or in any combination:

R_1 represents a C_{1-5} branched chain alkyl group;

R_2 represents methyl or ethyl;

R_3 is E-1-propenyl;

R_5 represents a hydroxy or a C_{1-5} alkoxy group;

c or a and c are double bonds;

X is oxygen or an NH group.

Examples of this preferred group are:

4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy] phosphonyl-3'-hydroxybutanoic acid;

4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy](R and S) methoxyphosphonyl-3'-hydroxybutanoic acid;

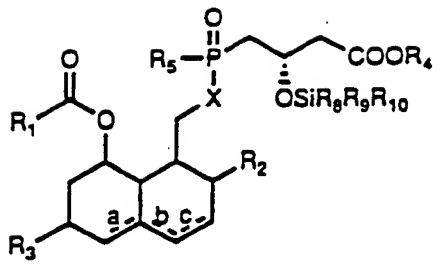
4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneamino] phosphonyl-3'-hydroxybutanoic acid,

or salts, particularly lithium salts, thereof.

Compounds of general formula I may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

(a) deprotecting a compound of general formula II



II

wherein,

R_1, R_2, R_3, R_4, R_5, X, a, b and c are as are as defined for general formula I; and

R_8, R_9 and R_{10} independently comprise C_{1-8} alkyl or phenyl;

using a nucleophilic desilylating agent;

(b) optionally after step (a), converting a compound of general formula I to another compound of general formula I.

Examples of suitable nucleophilic reagents for use in step (a) are sources of fluoride ions such as tetrabutylammonium fluoride in an inert solvent such as tetrahydrofuran and hydrofluoric acid in aqueous acetonitrile. With both these reagents, the reaction is preferably carried out at ambient temperature and when tetrabutylammonium fluoride is used as the

reagent, the reaction should be carried out in an inert atmosphere, for example nitrogen or argon and in the presence of an organic acid buffer such as acetic acid. However, other methods for the removal of silyl protecting groups are known and any of these may also be used.

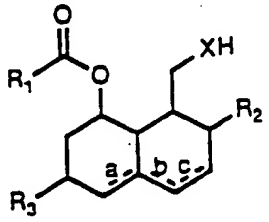
A compound of general formula I in which either or both R_4 or R_5 is an alkyl group can be converted to a compound in which both R_4 and R_5 are hydrogen atoms by hydrolysis using at least a 2-fold excess of a base. Any base can be used but hydroxylic bases such as lithium, sodium or potassium hydroxides or metal alkyl thiolates such as lithium or sodium methyl thiolate or sodium phenyl thiolate are particularly suitable.

The reaction temperature may be from 50°C to 80°C and any solvent may be used which boils at a temperature at least as high as the required reaction temperature and which dissolves both the starting material and the base. Suitable solvents include polar organic solvents such as methanol, ethanol, tetrahydrofuran, acetonitrile N,N-dimethylformamide, alone or mixed with water, or water itself. The hydrolysis is allowed to continue for at least twelve hours.

Compounds of general formula I in which both R_4 and R_5 are alkyl groups can be selectively hydrolysed to give compounds of general formula I in which R_4 is a hydrogen atom and R_5 is an alkyl group by mild hydrolysis with one of the bases mentioned above, although in this case, there should not be an excess amount of base. The polar organic solvents mentioned

above are also suitable for this mild hydrolysis reaction but the reaction temperature should be between 0°C and 50°C, preferably ambient temperature. The reaction proceeds to completion in about twelve hours.

Silyl ethers of general formula II wherein X is O or NH can be prepared by reaction of a compound of general formula III

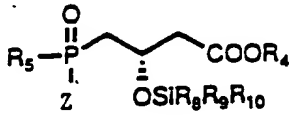


III

wherein

X is O or NH and

R_1, R_2, R_3, a, b and c are as defined in general formula I; with a compound of general formula IV



IV

wherein R_4 and R_5 are as defined in general formula I;

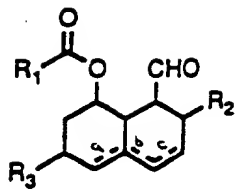
R_8, R_9 and R_{10} are as defined in general formula II; and

Z is hydroxy, fluoro, chloro or bromo.

When Z is fluoro, chloro or bromo, the reaction should be carried out under an inert atmosphere, for example nitrogen or argon, preferably at ambient temperature. The solvent for this reaction is preferably inert and basic, for example pyridine, but inert non-basic organic solvents such as dichloromethane or tetrahydrofuran may also be used although in this case, a mild organic base such as triethylamine or N-methyl morpholine must also be present.

When Z is a hydroxy group, the compounds of general formula II may be prepared by reaction of compounds of general formulae III and IV together with a condensing agent, for example dicyclohexanecarbodiimide (DCC) or water soluble derivatives thereof. In this case, the reaction should preferably be carried out in an inert solvent such as dichloromethane, tetrahydrofuran or pyridine. In place of DCC, it is possible to use other condensing agents such as carbonyldiimidazole.

Compounds of general formula IV are known and can be prepared by the method described in DE-A-3817375. Compounds of general formula III in which X is O are known and compounds of general formula III wherein X is NH can be prepared from compounds of general formula V



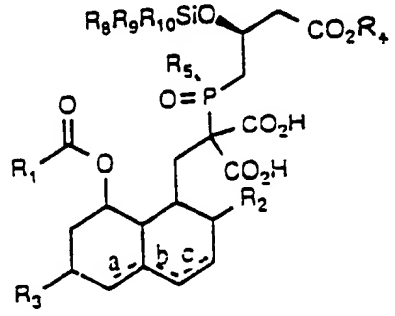
V

wherein R_1, R_2, R_3, a, b and c are as defined for general formula I;

by the method described in DE-A-3817375.

Compounds of general formula V are also known.

Compounds of general formula II wherein X is CH_2 can be prepared by decarboxylation of compounds of general formula VI



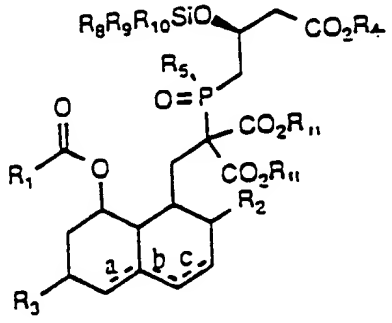
VI

wherein

a, b, c, R_1, R_2, R_3, R_4, R_8, R_9, and R_{10} are as defined above and R_5 is a C_{1-8} alkoxy group.

The decarboxylation reaction may be performed by any method known in the art, but preferred methods include heating a compound of general formula VI to a temperature of greater than 70°C in an inert, non-basic, relatively high-boiling solvent such as water, DMSO or DMF. The solvent may optionally contain ionic solutes for example alkali metal halides (eg sodium chloride in DMSO) or sodium bicarbonate (in DMF) which are known to promote decarboxylation reactions.

Compounds of general formula VI can be obtained by hydrolysis of compounds of general formula VII



VII

wherein

a, b, c, R, R_1, R_2, R_3, R_4, R_8, R_9 and R_{10} are as defined above;

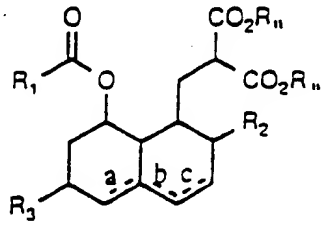
R_5 is a C_{1-8} alkoxy group; and

each R_{11} independently represents a hydrogen atom, a C_{1-5} alkyl (optionally substituted phenyl) group or the

two R_{11} groups may, together with the atoms to which they are attached, form a C_{6-8} cyclic system, for example an isopropylidene diester as in meldrums acid.

For the hydrolysis, any combination of base and solvent that is suitable for the hydrolysis of esters may be used, but preferred systems include lithium, sodium or potassium hydroxides or metal alkyl thiolates such as lithium or sodium methylthiolates or sodium phenyl thiolate. The reaction may be performed in a solvent which dissolves both the base and the substrate. Polar organic solvents are suitable for this purpose for example methanol, ethanol, THF acetonitrile, DMF or DMSO, alone or mixed with water or water itself. Optionally if R_{11} is an acid sensitive grouping such as a t-butyl ester, then acid hydrolysis methods such as are known in the art may be employed.

Compounds of general formula VII can be obtained by reaction of a compound of general formula VIII

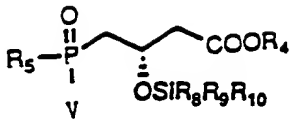


VIII

wherein

a, b, c, R_1, R_2, R_3 and R_{11} are as defined above;

with a compound of general formula X



X

wherein

R_4, R_8, R_9 and R_{10} are as defined above;

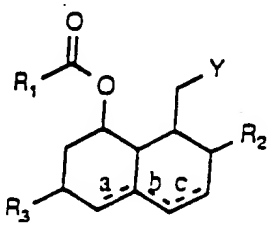
R_5 is a C_{1-8} alkoxy group;

V is fluoro, chloro or bromo.

The reaction may be performed by addition of a strong non-nucleophilic base to a compound of general formula VIII in a polar aprotic solvent between -78°C and ambient temperature to deprotonate the compound at a position alpha to the carboxylic ester groups. Once the malonate anion has been formed, a solution of a compound of general formula X in the same solvent is added to it between 0°C and ambient temperature, and the reaction mixture is heated at between 50 and 100°C until the reaction is complete. Suitable bases for the first step include sodium alkyl lithium reagents, sodium and potassium hydride, secondary alkyl lithium amides such as lithium diisopropyl amide and sodium and lithium hexamethyl disilazides. THF, dimethoxyethyl ether, DMF and DMSO are preferred solvents for this

transformation although other solvents could also be used. Compounds of general formula X can be prepared by methods described in DE-A-3817375.

Compounds of general formula VIII can be prepared from compounds of general formula IX



IX

wherein a, b, c, R_1, R_2 and R_3 are as defined in general formula I and Y is a leaving group, for example a chloride, bromine, or iodine atom, or a mesylate, tosylate or triflate group;

by reaction with an equivalent, or preferably an excess, of the anion of a malonic acid derivative in a suitable non-protic solvent.

The malonic acid derivative can be a monoalkyl-, or dialkyl- or arylester of malonic acid, and cyclic diesters such as meldrum's acid are also suitable. Lower alkyl diesters such as dimethyl and diethyl malonate lower alkyl monoesters such as monomethyl-, monoethyl- and mono-t-butyl- malonic acid are preferred since these reagents react more quickly and in higher yield.

The reaction is performed by addition of a strong non-nucleophilic base to a solution of the malonate compound in a non-protic solvent. For diesters, one equivalent of base to each equivalent of malonate compound should be used, but for monoesters of malonic acid, two equivalents of base for each equivalent of substrate should be employed. The deprotonation may be performed between -78°C and room temperature. Any base and solvent suitable for the deprotonation of compound VIII may be used for this step, although hexamethyldisilazide in THF is especially preferred. The reaction proceeds by adding a solution of a compound of general formula IX to a solution of the malonate anion in the same solvent and the reaction mixture is heated at between 50 and 100°C for at least 5 hours.

Compounds of general formula IX can be prepared from known compounds of general formula III where X is oxygen. Mesylates, tosylates and triflates of general formula IX may be prepared directly from alcohols of general formula III by reaction with the requisite sulphonyl chloride in a basic organic solvent such as pyridine or a non-protic solvent such as dichloromethane containing a mild organic base such as triethylamine at or below 0°C. Such transformations are known in the art. Halides of general formula IX may be prepared from these sulphonate esters by reactions also known in the art. For example an iodide of general formula IX may be prepared from the mesylate by heating it under reflux in methyl ethyl ketone containing 5 equivalents of sodium iodide for 18 hours.

Compounds of general formula II are valuable intermediates in the preparation of compounds of general formula I and therefore according to a third aspect of the invention, there is provided a compound of general formula II.

The compounds of general formula I are useful as anti-hypercholesterolaemic agents for the treatment of arteriosclerosis, hyperlipidaemia, familial hypercholesterolaemia and like diseases in humans. The invention therefore also relates to a method for the treatment of patients suffering from these diseases.

According to a further aspect of the invention there is provided a compound of general formula I for use in human or veterinary medicine, particularly in the treatment or prophylaxis of hypercholesterolaemia, hyperlipidaemia or arteriosclerosis.

According to yet a further aspect of the invention, there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of hypocholesterolaemia, hyperlipidaemia or arteriosclerosis.

Compounds of general formula I may be administered orally or parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to use the oral route. Doses may be varied, depending on the age, severity, body weight and other conditions of human patients but daily dosage for adults is within a range of from about 2 mg to 2000 mg (preferably 5 to 100 mg) which may be given in one to

four divided doses. Higher doses may be favourably employed as required.

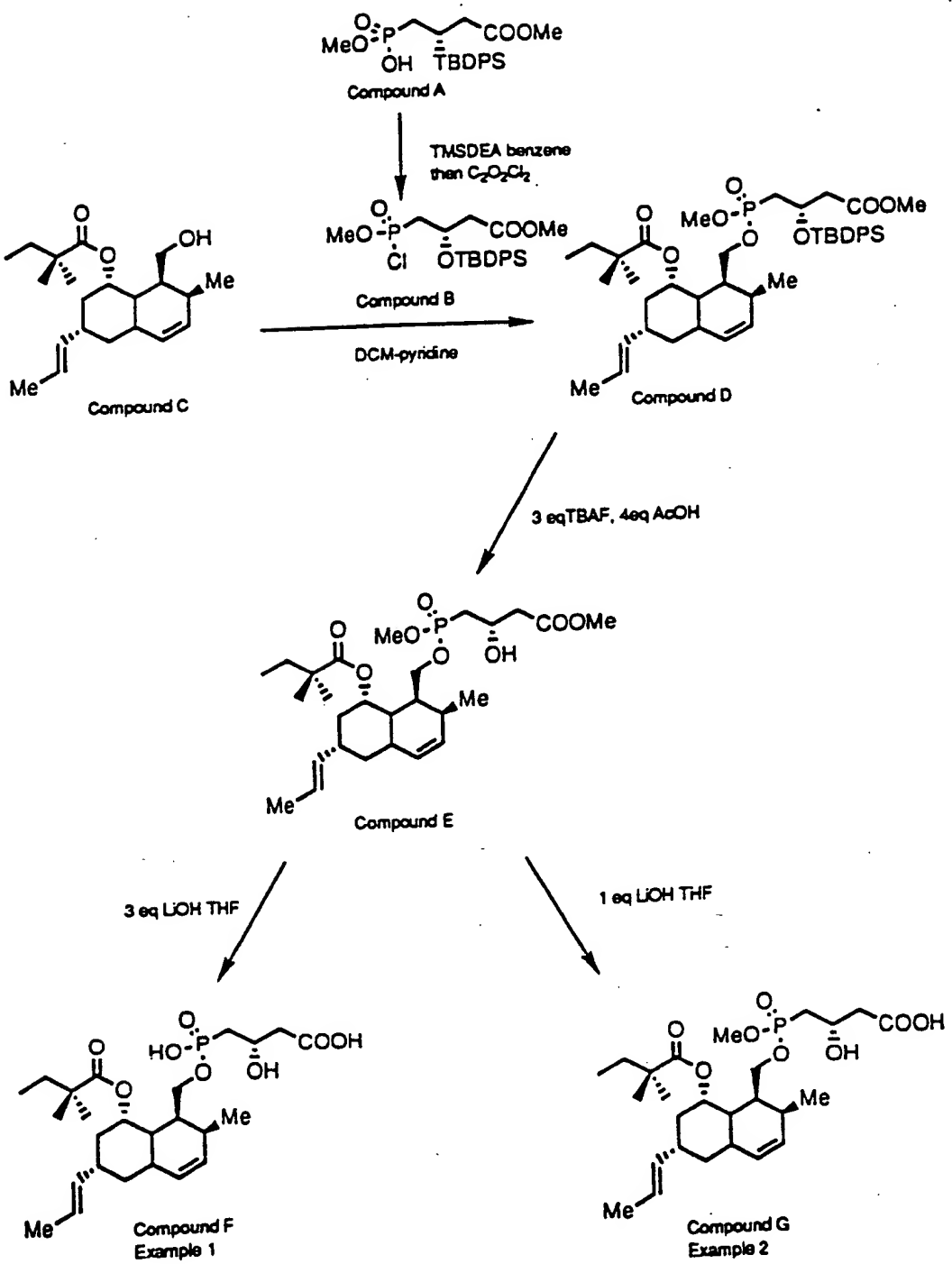
The compounds of this invention may also be co-administered with pharmaceutically acceptable non toxic cationic polymers capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract. Examples of such polymers include cholestyramine, colestipol and poly[methyl-(3-trimethylaminopropyl)- iminotrimethylene dihalide]. The relative amounts of the compounds of this invention and these polymers is between 1:100 and 1:15000.

The following examples show representative compounds encompassed by this invention and their syntheses (see Scheme 1). However, it should be understood that they are for the purposes of illustration only.

Organic solutions were dried over sodium sulphate or magnesium sulphate, and evaporated under reduced pressure. NMR spectra were recorded at ambient temperature in deuteriochloroform at 250 MHz for proton and 62.5 MHz for carbon unless noted otherwise. All chemical shifts are given in parts per million relative to tetramethylsilane. Infra red spectra were recorded at ambient temperature in solution in chloroform, or in the solid state in a potassium bromide disc as noted.

Chromatography was carried out using Woelm 32-60 μm silica.

Scheme 1


Compound A
TMSDEA benzene
then $C_2O_2Cl_2$
Compound B
DCM-pyridine
Compound C
Compound D
3 eqTBAF, 4eq AcOH
Compound E
3 eq LiOH THF
1 eq LiOH THF
Compound F
Example 1
Compound G
Example 2

Example 1

Step A

Methyl-(S)-3[1,1-dimethylethyl)-diphenylsilyloxyl-4-(chloromethoxyphosphinyl)-butanoate.

[compound B]

A stirred solution of methyl-(S)-3[(1,1-Dimethylethyl)-diphenylsilyloxy]-4-(hydroxymethoxyphosphinyl)-butanoate [compound A] (1.16 g, 2.56 mmol) (prepared by the method of DE-A-3817375) in 1:1 dry benzene (5 ml) and dichloromethane (5ml) was treated with trimethylsilyldiethylamine (1.16 ml, 6.1 mmol) at room temperature under argon. After 1 hr the solvent was evaporated under reduced pressure and the residue taken up in dichloromethane (5ml) containing 2 drops of DMF. The solution was cooled to -15°C and treated with oxalyl chloride (292 µl, 3.34 mmol). After 5 min at -15°C, the solution was allowed to warm to room temperature over 1 hr and then evaporated under reduced pressure to give crude methyl-(S)-3[1,1-dimethylethyl)-diphenylsilyloxy]-4-(chloromethoxyphosphinyl)-butanoate [compound B] (1.10 g) as a yellow oil.

Step B

Methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxyl-6[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]methoxy-phosphinyl-3'[1,1-dimethylethyl)-diphenylsilyloxyl-butanoate.

[compound D]

Crude phosphinyl chloride [compound B] (234mg, 0.496 mmol) was added in three portions of 115, 60 and 60mg

after 0, 15 and 40 hr respectively, to a stirred solution of (1S,2S,4aR,6S,8S,8aS)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-80[(2"-dimethyl-1"oxo-butyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)methanol [compound C] (50 mg, 0.149 mmol) (prepared by the method of patent WO-A-9100280) in 2:1 pyridine-dichloromethane (0.5 ml) at room temperature under argon. After 3 days the reaction mixture was diluted with dichloromethane (25 ml) and washed twice with 3N citric acid solution (2x20 ml). Drying over $MgSO_4$ and evaporation under reduced pressure gave a clear oil (240 mg) which was flash chromatographed on silica (8 g) under gradient elution [1:4 ethyl acetate-hexane to 2:3 ethyl acetate-hexane] to afford methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6- [(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy]methoxy-phosphinyl-3'[1,1-dimethylethyl)-diphenylsilyloxy]- butanoate [compound D] (37 mg, 0.052 mmol, 35% yield) as an oil.

TLC 40% ethyl acetate-hexane Rf = 0.25 U.V. and PMA.

Step C

Methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2, 4a, 5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy]methoxyphosphinyl-3'-hydroxy-butanoate. [compound E]

The silyl ether [compound D] (74 mg, 0.096 mmol) was stirred for 18hr at room temperature under argon in a solution of dry THF (1.2 ml) containing tetrabutyl-

ammonium fluoride (0.29 mmol) and acetic acid (0.38 mmol). The reaction mixture was diluted with diethyl ether (20 ml) and washed with water (20 ml) then saturated sodium carbonate solution (20 ml) and dried over MgSO4. Flash chromatography of the concentrated residue using 1:1 ethyl acetate-hexane increasing to ethyl acetate gave the title compound as an oil.

Yield (29 mg, 0.055 mmol) 61%

TLC Ethyl acetate Rf 0.38

δH ($CDCl_3$) 0.84(3H, t, J 7.3 Hz); 0.94(3H, d, J 6.4 Hz); 1.16(6H, 2s); 1.17-2.17(14H, m); 3.71(3H total - 2 isomers at phosphorus, 2d, J 10.9 Hz); 3.73-4.4(7H, m); 5.6-5.8(2H,m).

δC ($CDCl_3$) 176.8, 176.2, 134.6, 130.9, 121.6, 68.0, 63.4, 62.8, 51.3, 42 approx, 41.5, 38.1, 36.4, 36.3, 35.8, 34.5, 33.8, 31.5, 29.9, 29.7, 29.5, 23.2, 16.5, 14.3, 14.0, 11.1, 7.8.

Example 2

4'-[1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxyl-phosphonyl-3'-hydroxy-butanoic acid.

[compound F]

Compound E from Example 1 (14.5 mg, 2.9 x 10^{-5}M) was heated at 50°C for 16 hr with three equivalents of lithium hydroxide (2 mg, 8.7 x 10^{-5}M) in THF (1.1 ml).

The crude reaction mixture was chromatographed on two analytical 1mm kieselgel 60 plates (elution with 7:3 isopropanol- NH_4OH_{aq}) to give the title compound as an oil (7 mg, 1.4×10^{-5}M).

Yield 48%.

TLC eluant 7:3 i-PrOH:NH_4OH_{aq} Rf = 0.51 U.V. only.

δH ($CDCl_3$) 0.95(6H, s); 1.2-2.1(19H, m); 3.8(1H, m); 4.4(3H, m); 5.05-5.8(5H, m).

Example 3

4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6, 7, 8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxyl-R and S-methoxyphosphinyl-3'-hydroxybutanoic acid.
[compound G]

Compound E from Example 1 (14.5 mg, 2.7×10^{-5}M was stirred for 16 hr in tetrahydrofuran (0.4 ml) containing 1.2 equivalents of lithium hydroxide (3.5×10^{-5}M). The neat solution was thin-layer chromatographed on two 10 x 20 cm Kieselgel 60 analytical plates eluting with 7:3 isopropanol-2N aqueous ammonia solution to give the desired compound as an oil (13 mg, 2.5×10^{-5}M).

Yield 93%.

TLC eluant 7:3 i-PrOH:NH_4OH_{aq} Rf 0.68.

δH ($CDCl_3$) 0.84(3H, t, J 7.3Hz); 0.94(3H, d, J 6.4Hz); 1.16(6H, 2s); 1.17-2.17(14H, m); 2.5(4H, m); 3.71(3H total, 2d, J 10.9Hz for each POMe); 3.73-4.4(7H, m); 5.60-5.8(2H, m).

δC ($CDCl_3$) 176.8, 176.2, 134.6, 130.9, 121.6, 68.0, 63.4, 62.8, 51.3, 42 approx, 41.5, 38.1, 36.4, 36.3, 35.8, 34.5, 33.8, 31.5, 29.9, 29.7, 29.5, 23.2, 16.5, 14.3, 14.0, 11.1, 7.8.

The intrinsic HMG-CoA reductase inhibition activity of the claimed compounds is measured in the in vitro protocols described below.

Example 4 - Pharmacology

IN VITRO DETERMINATION OF INHIBITORY POTENTIAL OF HMG-CoA REDUCTASE INHIBITORS.

HMG-CoA reductase was induced in rats by feeding a normal diet supplement with 3% cholestyramine resin for one week prior to sacrifice. The livers were excised from the sacrificed rats and microsomal pellets prepared by the method of Kleinsek et al, Proc. Natl. Acad. Sci. USA, 74 (4), pp 1431-1435, 1977. Briefly, the livers were immediately placed in ice-cold buffer I (see below) and homogenised in a Potter-Elvehjem type glass/TEFLON homogeniser (10 passes at 1000 rpm).(The word TEFLON is a trade mark). The homogenate was centrifuged at 100,000 x g for 75 minutes, the microsomal pellet resuspended in buffer II (see below) and centrifuged at 100,000 x g for 75 minutes. The resultant pellet was stored at -70°C until required for

assay purposes. The compositions of buffers I and II are given below.

Buffer I	Buffer II
50 mM KPO_4 pH 7.0	50 mM KPO_4 pH 7.0
0.2 M sucrose	0.2 M sucrose
2 mM DTT	2mM DTT
	50 mM EDTA

Assay of HMG-CoA Reductase Activity and Determination of Activity of Inhibitors

Membrane bound enzyme isolated as above is used for determining the activity of inhibitors. The assay is performed in a total volume of 300 µL in 100 mM KPO_4 pH 7.2 buffer, containing 3 mM $MgCl_2$, 5 mM glucose-6-phosphate, 10 mM reduced glutathione, 1 mM NADP, 1 unit glucose-6-phosphate dehydrogenase, and 1 mg/mL BSA, with resuspended enzyme. Putative inhibitors are dissolved in dimethylsulphoxide and 10 µL aliquots added to the incubation.

The assay is pre-incubated at 37°C for 10 minutes and initiated by the addition of 0.1 µCi 3-hydroxy-3-methyl-[3-^{14}C]glutaryl coenzyme A (52 Ci/Mole) followed by incubating the complete reaction at 37°C for 10 minutes. At the end of this period the reaction is stopped by adding 300 µL of a 10 mM mevalonolactone solution in 0.1 M hydrochloric acid and the mevalonic acid product allowed to lactonise for a further period of 30 minutes. The product is then isolated by

chromatography using Bio-Rex 5 resin and the enzyme activity quantified by liquid scintillation spectrophotometry.

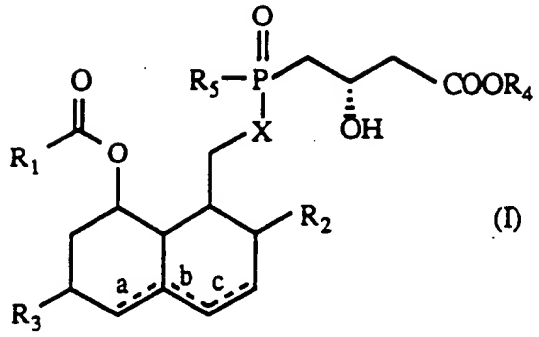
Appropriate controls are included in the assay and IC_{50} values obtained by graphical means.

Representative IC_{50} values for compounds F and G in the isolated enzyme assay were 11 and 2900 nanomoles respectively. In this assay, the IC_{50} value for dihydromevinolin was 30 nanomoles.

Included within the scope of this invention is the method of treating arteriosclerosis, familial hypercholesterolaemia or hyperlipidaemia which comprises administering to a subject in need of such treatment a non toxic therapeutically effective amount of the compounds of formulae I or II or pharmaceutical compositions thereof.

CLAIMS

1. A compound of general formula I:



(I)

wherein

R_1 represents a C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-8})alkyl, C_{2-8} alkenyl, optionally C_{1-6} alkyl substituted phenyl, or optionally substituted phenyl(C_{1-6} alkyl) group;

R_2 represents C_{1-8} alkyl group;

R_3 represents a C_{2-6} alkenyl group or a C_{2-6} alkenyl group linked to an optionally substituted phenyl group;

R_4 represents a hydrogen atom, a C_{1-5} alkyl group, a C_{1-5} alkyl group substituted with a group chosen from optionally substituted phenyl, dimethyl amino or acetylamino; or a group M;

R_5 represents a hydroxyl, -OM, or C_{1-8} alkoxy group;

M represents a cation capable of forming a pharmaceutically acceptable salt;

X represents an oxygen atom, NH group or CH_2 group;

a, b and c represent independently single or double bonds except that when a or c are double bonds then b represents a single bond;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in claim 1 wherein R_1 is a C_{1-5} branched chain alkyl group.

3. A compound as claimed in claim 1 or claim 2 wherein R_2 is a methyl or an ethyl group.

4. A compound as claimed in any one of claims 1 to 3 wherein R_3 is E-1-propenyl.

5. A compound as claimed in any one of claims 1 to 4 wherein R_5 is a hydroxy or a C_{1-5} alkoxy group.

6. A compound as claimed in any one of claims 1 to 5 wherein c or a and c are double bonds.

7. A compound as claimed in any one of claims 1 to 6 wherein X is oxygen or an NH group.

8. 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-

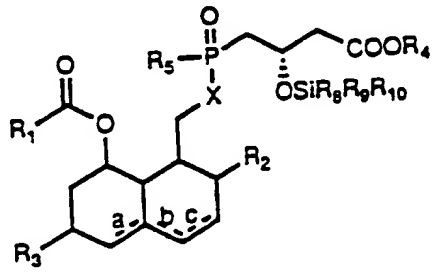
[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]phosphonyl-3'-hydroxybutanoic acid;

4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy](R and S) methoxyphosphonyl-3'-hydroxybutanoic acid; or

4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneamino] phosphonyl-3'-hydroxybutanoic acid.

9. A process for the preparation of a compound as claimed in any one of claims 1 to 8, the process comprising

(a) deprotecting a compound of general formula II



II

wherein

R_1, R_2, R_3, R_4, R_5 and X are as defined in claim 1; and

R_8, R_9 and R_{10} independently comprise C_{1-8} alkyl or phenyl;

with a nucleophilic desilylating agent;

(b) optionally after step (a) converting a compound of general formula I to another compound of general formula I.

10. A process as claimed in claim 9 wherein the nucleophilic deprotecting agent comprises a source of fluoride ions, for example tetrabutylammonium fluoride or hydrofluoric acid.

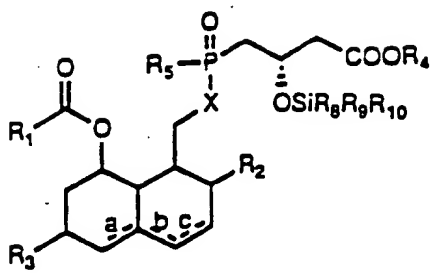
11. A compound as claimed in any one of claims 1 to 8 for use in medicine.

12. The use of a compound as claimed in any one of claims 1 to 7 in the preparation of an agent for the treatment or prophylaxis of hypocholesterolemia, hyperlipidaemia or arteriosclerosis.

13. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 8 together with a pharmaceutically or verterinarily acceptable excipient.

14. A composition as claimed in claim 13 further including at least one pharmaceutically acceptable non-toxic cationic polymer capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract.

15. A compound of general formula II



II

wherein R_1, R_2, R_3, R_4, R_5 and X are as defined in claim 1; and

R_8, R_9 and R_{10} independently comprise C_{1-8} alkyl or phenyl.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 92/02226

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07F 9/40, A61K 31/66
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE, A1, 3817375 (E.R. SQUIBB & SONS, INC.), 8 December 1988 (08.12.88), see page 9 line 24 - page 10 line 24 and example 15	1-15
Y	WO, A1, 9100280 (BRITISH BIO-TECHNOLOGY LIMITED), 10 January 1991 (10.01.91), see pages 1-7 and 41-84	1-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 1993	03 MAR 1993
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer GÖRAN KARLSSON

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 92/02226

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR, A1, 2596393 (SANOFI, SA), 2 October 1987 (02.10.87), see the whole document	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

08/01/93

International application No.
PCT/GB 92/02226

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A1- 3817375	08/12/88	AU-B- 610591	23/05/91
		AU-A- 1650888	24/11/88
		CH-A- 676984	28/03/91
		FR-A- 2615508	25/11/88
		GB-A,B- 2205837	21/12/88
		GB-A- 2235924	20/03/91
		JP-A- 1056689	03/03/89
		NL-A- 8801330	16/12/88
		SE-A- 8801903	23/11/88
		US-A- 4904646	27/02/90
		US-A- 5017716	21/05/91
WO-A1- 9100280	10/01/91	AU-A- 6032290	17/01/91
		EP-A- 0480986	22/04/92
		JP-T- 4506523	12/11/92
FR-A1- 2596393	02/10/87	NONE	